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09/218,277	12/22/1998	MICHAL EISENBACH-SCHWARTZ	EISHENBACH=3A	3311

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EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/218,277	Applicant(s) Elsenbach-Schwartz
	Examiner Sharon L. Turner, Ph.D.	Art Unit 1647

-- The MAILING DATE f this communication appears on the cover sh t with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 1-27-02

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 3-7, 9, 11-13, and 16-20 is/are pending in the applica

4a) Of the above, claim(s) 9-13, 16-20 to the extent of the non-elected invention is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 3-7, 9, 13, and 16-20 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 3-7, 9, 11-13, and 16-20 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-28-02 has been entered.

2. The amendment filed 12-27-01 has been entered into the record and has been fully considered.

3. Claims 3-7, 9, 11-13 and 16-20 are pending.

4. Applicant's continued traversal of the Restriction requirement set forth in Paper No. 13, mailed 8-15-00 and Paper No. 23, mailed 12-27-01 appears moot as the restriction requirement was made final in Paper No. 15, mailed 12-15-00. If applicant wishes to pursue the matter further they should file a petition in accordance with 37 CFR 1.144.

However, to further clarify the record applicants response 3-5-01 directs that the examiner has maintained the restriction in that the claims of Group I and Group II achieve different effects as claimed, may be differently classified and require different searches. Applicants continued traversal states that the examiner is incorrect in stating that the two groups as claimed in claim 16 are separable in that they achieve different effects as claimed. This argument is based on applicant's rewording of claim 16 such that the methods of Group I and

Group II are now recited together in a single claim. Applicants further contend that as claim 16 is a valid generic claim, both groups and all species must be examined once the generic claim is found allowable.

In response the examiner notes that applicants newly presented claim 16 in fact recites the method of Group I and Group II in a single claim. However such recitation does not negate the fact that the claim is separable as defined in the restriction of 8-15-00. The different methods achieve different effects, may be differently classified and require different search and examination considerations. A reference for one would not necessarily be a reference for the other. The two methods are drawn to 1) preventing or inhibiting axonal *degeneration* and 2) promoting nerve *regeneration.* The methods are separable as evidenced by the following literature references which establish a separate status in the art of *axonal regeneration* and *axonal degeneration* which are diametrically opposed processes and are patentably distinct as evidenced by Plata-Salaman et al., (1991) Peptides 12(3):653-63, George et al., (1995) J. of Neuroscience 15(10):6445-52, Petrovich et al., (1997) 19(5):551-4, Bradbury et al., (1998) Eur. J. of Neurosci., 10(10):3058-68, Pan et al., (1997) Neurosci. & Biobehav. Reviews 21(5):603-13 and Wang et al., (2000) J. of Neuropath. & Exp. Neurol., 59(7):599-606. The methods may be separately classified for example in class 435, subclasses 374, 375 or 377. The search and examination of both groups together represents a burden to the examiner, regardless of any similarity in reagents or steps. Thus, it is further noted that as such the claim is not properly generic as the methods do not share the characteristics of a genus, i.e., a common utility or

function. Alternatively, the claims define distinct methods with different use, different modes of operation, different function and different effects, see in particular MPEP 803.02 and 806.04. It is also noted that no claim is indicated allowable and thus applicants are not presently entitled to the search and examination of any other group or species of the claimed invention.

Applicants response of 12-27-01 further argues that the preamble statement "preventing or inhibiting axonal degeneration and/or promoting nerve regeneration" is a statement of intended mechanism, that whatever happens, happens whether it is stated in the preamble of the claim or not and that anyone administering the composition to a person having such a defined injury or disease will inherently achieve prevention or inhibition of axonal degeneration and/or promotion of nerve regeneration. Applicants further argue that issuance of two patents to such delimited claims would constitute issuance of two patents to the same invention.

In response to applicant's arguments filed 12-27-01, it is noted that the claim recitations noted by applicant's are within the preamble of the claim and thus obtain consideration as patentable weight, and thus a reference to one mechanism would not necessarily encompass (under 35 USC 102 and 103) the other. Applicant's do not appear to be conceding the point that a reference to inhibiting axonal degeneration, for example, would render promoting nerve regeneration, obvious. In any case, the generic claim is not deemed allowable or free from the prior art. Upon the determination of allowable subject matter, the Examiner would reconsider rejoinder depending upon the terms of the claims.

Again, the requirement is still deemed proper and is therefore made FINAL.

5. Claims 9-13, and 16-19 in part are withdrawn as set forth in Paper No's 15 and 19 from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The elected species is to a method of delivering antigen, specifically Myelin Basic Protein antigen of SEQ ID NO:12. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

6. Newly submitted claim 20 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 20 appears to be a substantial duplicate of canceled claim 10. The claim is withdrawn to the extent of the nonelected invention, for the same reasons of record as set forth above for claim 10, the combination/sub-combination being separable and the elected invention being limited to the extent of the MBP antigen as set forth above..

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 20 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

7. Claims 3-7, 9, 13, and 16-20 are objected to under 37 CFR 1.75(c), as being drawn to nonelected subject matter and thus to multiple, patentably distinct inventions.

Applicant's argue as set forth above that the inventions are not patentably distinct.

Applicant's arguments filed 12-27-01 have been fully considered but are not persuasive as set forth above. The inventions are drawn to multiple patentably distinct inventions with different methods, reagents, steps, outcomes and mechanisms, in particular, M.P.E.P. 803.02 states that:

> "Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

Claim Rejections - 35 USC § 112

8. Claims 3-7, 9, 13 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant's have amended claim 16 to recite "wherein said injury or disease is other than an autoimmune disease or a neoplasm." Yet the specification does not appear to support the recitation and applicant's have not pointed to such support. Thus, the recitation appears to be new matter absent evidence for its' support. It is noted that in contrast to the

claims, the exemplary embodiments of the invention are at least partially framed in EAE, autoimmune animal models, see in particular Example 7.2.2, p. 37 and Figure 4.

9. Claims 3-7, 9, 13 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant's claims have been amended from the generic of any disease or injury to the sub-generic of diseases and injuries "other than an autoimmune disease or neoplasm." Yet Applicant's specification does not evidence that Applicants were in possession of the methods for the sub-generic class, nor does the specification describe this sub-generic class such that the skilled artisan is apprised of the members of the sub-genus in comparison to the genus. Thus, the recitation appears to lack adequate written description to show that Applicants were in possession of sub-genus and its inclusive and exclusive members at the time of filing. Thus, the claims lack adequate written description under 35 USC 112, first paragraph.

10. Claims 4-7, 9, 13 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ameliorating degenerative effects consistent with Example 9 in crush injury of rat optic nerve, ischemia and in injuries associated with ischemia as claimed in claim 3 does not reasonably provide enablement for

the broad but sub-generic recitation of ameliorating the degenerative effects of injury or disease, wherein said injury or disease is other than an autoimmune disease or a neoplasm. It is noted that neurodegenerative effects consistent with Example 9, crush injury include neurodegenerative effects due to ischemia as crush injury is not a severing of the axonal connections in the optic nerve but yet the injury is consistent with perturbation of the blood flow to the area, i.e., ischemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, in particular for alternative diseases not largely associated with crush trauma or ischemia, for example glaucoma, Alzheimer's etc., as claimed in claim 4 and for example hearing loss or mental retardation.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The scope of the claims encompass amelioration of degenerative effects of injury or disease on the CNS or PNS wherein the injury or disease is other than an autoimmune disease or a neoplasm. Thus the scope encompasses at least those diseases as recited in the dependent claims not expected to be commensurate with either crush injury or ischemia including those of diabetic neuropathy, senile dementia, Alzheimer's, Parkinson's,

glaucoma, Huntington's, ALS, vitamin deficiency, but also for example, hearing deficits, color blindness and mental retardation. The effects encompassed by these diseases are thus broad including for example, neuritic plaques, aberrant sugar regulation, insulin insensitivity, motor dysfunction, intraocular pressure, blurred vision, blindness, pain, sensory deficits, memory deficits and cognitive deficits, which effects are not commensurate with ischemia and crush injury.

The specifications guidance (with respect to administration of MBP) is limited to the example of crush injury of rat optic nerve and inhibition of secondary (Wallerian) degeneration as indicated by an about 1.3 greater fold number of labeled retinal ganglion cells in MBP treated animals as compared to controls. Yet the etiology and pathology of ischemia and crush injury are largely dissimilar and would not be expected by the artisan to benefit for example, diabetic neuropathy, senile dementia, Alzheimer's, Parkinson's, glaucoma, Huntington's, ALS, vitamin deficiency, hearing impairments, color-blindness or mental retardation and thus these diseases are not commensurate in scope with those degenerative effects noted for example in neuronal crush models or in ischemia.

Further, the art is unpredictable in the requirements necessary for the amelioration of degenerative effects including neuronal degeneration sufficient to restore function, see for example Liuzzi et al., Neurosurg. Clin. N.A., 2(1):31-42, 1991 with respect to peripheral nerve regeneration, Jackowski et al., Br. J. Neurosurg., 9:303-317, 1995 with respect to CNS regeneration and Morris et al., Neurology, 39:1159-65, 1989 with respect to

defects/deficits associated with Alzheimer's Disease. For example, one of skill in the art would not expect a decrease in secondary (Wallerian) degeneration to be necessarily indicative or predictive of restoration of sensory and motor function, cognition or memory as encompassed by the generic claim.

Thus, the artisan is not readily assured of amelioration of the scope of effects recited in the preamble (amelioration of the (generically claimed) degenerative effects of injury or disease on the CNS or PNS, wherein the injury or disease is other than an autoimmune disease or neoplasm) without the requirement for further undue experimentation to define those effects more likely than not ameliorated in response to MBP antigen treatment.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 3-7, 9, 13 and 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants claim structure recites administering to a human having an injury or disease wherein the injury or disease encompasses all injuries and diseases with the exception of when the injury or disease is an autoimmune disease or neoplasm. Yet the specification fails to readily distinguish the metes and bounds of the injuries or diseases included or excluded from the claim. While the skilled artisan recognizes several diseases which may appear to fall in one category or

the other, the art recognizes multiple diseases which may be viewed as autoimmune in nature which appear to be encompassed by dependency in applicant's claims. In particular, Weiner et al., US 5,858, 364 of record recognizes a list of autoimmune diseases including diabetes and diabetic neuropathy. Thus, diabetes for example would appear to be excluded, yet claim 4 specifically recites diabetic neuropathy and glaucoma which are recognized as degenerative effects of diabetes, see in particular Weiner et al., column 6, lines 41-49 and Merck Manual, Yucel and Enoch, each of record. Thus, the metes and bounds of the encompassed effects, injuries and diseases appears to be indefinite as claimed. Clarification is required. It is noted that many effects of neurodegeneration as a genus cross the sub-generic class of diseases which may be classified as autoimmune in nature. For example, diabetes (diabetic neuropathy) may produce deficits in sensory and motor function similar to trauma, see in particular Enoch and Yucel, of record. (Alternatively, applicant's dependent claims do not further limit, but broaden)

Priority

13. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Israel on 5-19-98. Applicant has filed a certified copy of the application as required by 35 U.S.C. 119(b), received as Paper No. 18, 5-16-01.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 3, 5-7, 9, 13, 16-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al., PNAS 94:10873-10878, September 1997, and The Merck Manual, Merck & Co., Inc., 1992, pp. 1510-11, 1518-23, 110-11, 412-13 and 1452-59

Becker et al., teach administration of myelin basic protein (MBP) to decrease stroke size (neuronal degeneration or to promote regeneration of CNS neurons) after transient focal cerebral ischemia. Ischemia is not deemed an autoimmune disease or neoplasm as the cause is occlusion of blood flow and not an autoimmune disease or a neoplasm. Thus, the injury or disease of ischemia is within the scope of the injuries and diseases as encompassed by the generic claim. In particular, ischemia is widely recognized in the injuries of claim 3, including blunt trauma, penetrating trauma hemorrhagic stroke, ischemic stroke and damages caused by surgery due to a lack of blood flow. Becker et al., teach administration of MBP via repetitive gavage with 1 mg

of protein in 0.5 ml of PBS every 2-3 days for 2 weeks (a total of 5 feedings), and by injection with 50 ug in 50 ul of PBS with equal amounts of complete Freund's Adjuvant, see in particular, Materials and Methods, p. 10873, column 2. The administration is deemed an effective amount as the activity reducing neuronal degeneration and/or of promoting regeneration is provided, see in particular Figures 2 and 3 wherein infarct size is reduced. The treatment ameliorates degenerative effects such as neuronal degeneration and cell death within the infarct.

Becker et al., does not specifically teach administration in humans.

However, Becker et al., does teach that other species including humans can be tolerized, see in particular Conclusions, p. 10877. Becker suggests that humans can be orally tolerized and administration of MBP to humans has been proven to be safe. Thus, Becker suggest that it is conceivable that MBP can be used to treat patients at risk of ischemia for example with cerebrovascular disease. As evidenced in the Results, Discussion and Conclusion sections, Becker et al., teach the similarity of the immunologic responses of rats to humans in response to ischemia and as recognized in the art, animal models including the rat transient focal ischemia model is used as a model to predict relative outcomes to similar pathologic injury or disease in humans.

Moreover, the Merck Manual, 1992, pp. 1510-11, 1518-23, 110-11, 412-13 and 1452-59 teach the recognition of ischemia in humans and similarity in pathology including after injury or trauma and in diseases such as stroke.

Thus, it would have been prima facie obvious to the skilled artisan that the administration of MBP to ameliorate the degenerative effects of ischemia could also be used to ameliorate degenerative effects largely due to ischemia for example in injuries and diseases including blunt trauma, penetrating trauma hemorrhagic stroke, ischemic stroke and damages caused by surgery due to a lack of blood flow. One of skill in the art would have expected positive results based on the cumulative reference teachings of such utility as evidenced by Becker et al., and the similarity in the pathology of ischemia between rats and humans as evidenced by Becker and the Merck Manual. In addition, one of skill in the art would be motivated to administer MBP based on the beneficial results of Becker and the recognition in the art that ischemia is prevalent, if not causative in the noted neurologic diseases. One of skill in the art would have an expectation of success in such treatments as the patients rats of Becker exhibit decreased infarct size and neuronal degeneration. The artisan would clearly recognize that the patients and symptomatology coincide to each other. Thus, the reference teachings render the claimed invention drawn to the amelioration of degenerative effects obvious with respect to ischemia and the noted injuries as recited in claim 3 which are associated with ischemia.

Status of Claims

16. No claims are allowed.

Conclusion

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
March 18, 2002

Gary L Kunz

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